AF/1626

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 040283/0182

In re patent application of

David R. Adams et al.

Serial No. 09/600,631

Filed: February 12, 2001

Group Art Unit: 1626

Examiner: R. Anderson

For: AZETIDINE CARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

REQUEST FOR RECONSIDERATION UNDER 37 CFR § 1.116

Commissioner for Patents
Mail Stop AF
Washington, D.C. 20231

Sir:

This is a response to the Official Action mailed April 14, 2003 in connection with the captioned application.

Rejections Under 35 USC §103(a)

Claims 1-17 and 23-28 are rejected under 35 USC § 103(a) as unpatentable over GB 872447 and EP0194112. In response this rejection, applicants submitted a first 132 Declaration by Nathaniel Julius Monck showing nonobvious and unexpected results of the invention. Applicants contend that this previous Declaration asserted, contrary to the Examiner's interpretation of the experimental data and related statistics, that one of skill in the art would recognize that the data generated by the inventors evidence unexpected results that would not be predicted based on the prior art. Notwithstanding the submission of this previous Declaration, the Examiner has maintained the rejection under Section 103.

The Examiner's arguments can be summarized as follows. (1) The comparative data of the previous Declaration include only one Example (Ex. 20; R^1 = 4-$CF_3C_6H_4$) from the claims. (2) Because of the overlapping confidence limits, the Examiner still considers that no significant effect has been demonstrated. (3) The Examiner considers that the specification as filed does not state a preference for the substituted phenyl compounds now claimed (*i.e.* Ex. 20).

With regard to point (3), applicants respectfully urge that there is a clear preference for substituted groups in the specification. At page 5, lines 20-24, the specification states:

> "preferably R^1 is a substituted or unsubstituted aryl group selected from phenyl or naphthyl, more preferably R^1 is a substituted phenyl or naphthyl, more preferably R^1 is phenyl or naphthyl having 1 to 3 substituents and most preferably R^1 is phenyl or naphthyl having 1 or 2 substituents".

The Examiner should be well aware that certain sub-ranges of the generic scope of an application as filed are often more preferable than others, and it is the applicant's right to claim these preferred sub-ranges if so desired.

With regard to point (2), applicants respectfully submit that the Examiner is not correctly interpreting the significance of the statistical analysis, which is why she does not accept that a statistically significant effect is demonstrated. This is a completely opposite conclusion to that which would be reached by one of ordinary skill in the art when reading these data. In the present data set, "significance" is dependent upon whether the confidence limits of an ED_{50} of a test compound overlap with that of the vehicle. In Table 1 in Nathaniel Monck's earlier Declaration of 2nd January 2003, the test compounds whose ED_{50} confidence limits overlap with those of the vehicle do not show a significant effect. The compounds whose confidence limits do not overlap with that of the vehicle do show a significant effect, and these are marked with an asterisk.

Thus, the prior art compound 1-carbamoyl-3-phenylazetidine shows no significant effect at 15 mg/kg since its ED_{50} overlaps with that of the vehicle. In contrast, Example 20 at the same dosage does show a significant effect since its ED_{50} does not overlap with that of the vehicle. It is not relevant that the ED_{50} values of Example 20 overlap with the prior art compound. The important point is that the prior art compound is not statistically different from the vehicle, whereas Example 20 is statistically different. Example 20 is therefore clearly superior to the prior art compound.

With regard to point (1) above, the applicants have been able to provide additional data measured using the assay described on pages 13-14 of the specification. Table 1 below contains data which were not originally presented in the specification as filed, and relate to

specific Examples already included in the present application, as well as prior art compounds which contain an unsubstituted aryl group. These new data are incorporated into a second Declaration from Nathaniel Monck, attached hereto.

Table 1: Antagonism of 3-MPA-Induced Seizures

Compound	SC	SV
1-carbamoyl-3-phenylazetidine (GB-872447)	22.9	18.5
1-carbamoyl-3-naphthylazetidine	22.9	18.0
Example 11; R^1 = 3,4-dichlorophenyl	42.8	22.1
Example 12; R^1 = 3,4-dichlorophenyl	45.8	22.1
Example 13; R^1 = 3,4-dichlorophenyl	31.5	13.6
Example 16; R^1 = 4-trifluoromethylphenyl	44.2	13.6
Example 17; R^1 = 3-trifluoromethylphenyl	129.7	15.6
Example 18; R^1 = 3-trifluoromethylphenyl	54.6	15.6
Example 23; R^1 = 3-chloro-4-fluorophenyl	27.2	13.6
Example 25; R^1 = 3,4-difluorophenyl	45.8	17.7
Example 26; R^1 = 3-chloro-4-fluorophenyl	49.9	16.2
Example 28; R^1 = 3-trifluoromethyl-4-fluorophenyl	94.4	17.7
Example 29; R^1 = 3-chlorophenyl	129.3	18.6

SC = seizure threshold after treatment with test compound
SV = seizure threshold in vehicle treated group

It can be seen from the Table above that the compounds of the present invention show a significant improvement over the unsubstituted prior art compounds since they significantly increase the dose of 3-MPA to initiate a seizure response. There is nothing in the prior art that would suggest to one of ordinary skill in the art that the substituted compounds would show this improvement. Accordingly, applicants submit that they have demonstrated non-obvious unexpected results for the compounds of the present invention.

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional extension(s) of time are required for the filing of this paper, applicants expressly petition for such extension(s) and authorize the Commissioner to charge any deficiency to Deposit Account 19-0741.

Respectfully submitted,

July 14, 2003
Date

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.